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COMMENTARY

In search of an effective obesity treatment: A shot in the dark or a shot in the arm?

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Stedman's Medical Dictionary defines "epidemic" as the occurrence of an illness, specific health-related behavior, or other health-related events clearly in excess of normal expectancy. Defined as such, many consider obesity to be an epidemic in the United States. This alarming increase in both obesity prevalence and severity also is occurring worldwide. Vaccination has been an extremely effective method of curbing more "traditional" epidemics caused by viruses and bacteria. In this issue of PNAS, Zorrilla *et al.* (1) present results from studies using a vaccination approach to potentially fight the epidemic of obesity.

The Hormone Ghrelin

Specifically, Zorrilla *et al.* (1) developed a vaccination strategy designed to neutralize the actions of the orexigenic hormone

ghrelin. Ghrelin is produced primarily by endocrine cells of the stomach and gastrointestinal tract (2). Although ghrelin acts on many systems, including those modulating growth hormone release, gastrointestinal motility, insulin secretion, and insulin sensitivity, it is ghrelin's ability to act in the CNS to reverse states of energy insufficiency that has received the most attention (2–5). For instance, ghrelin levels rise before meals and in association with hunger (6). Ghrelin administration potently stimulates feeding and lowers energy expenditure (7–9). In addition, ghrelin shifts food preference toward diets rich in fat and at the same time shifts fuel preference away from metabolic utilization of fat as an energy source (7, 10). Ghrelin also increases the mRNA expression of many fat storage-promoting enzymes in white adipocytes and also may engage mesolimbic reward circuitry to increase the motivation to obtain food (11, 12). Chronic ghrelin administration eventually results in increased body weight gain and adiposity (7, 8). Collectively, these data have led to the hypothesis that inhibition of ghrelin action may be a feasible strategy to reduce body weight and food intake.

The Newly Described Obesity Vaccine

The strategy used by Zorrilla *et al.* (1) specifically targeted the acylated form of ghrelin as opposed to the des-acyl form (13). This difference is important because ghrelin is the only known peptide that is posttranslationally modified by the addition of an *n*-octanoic acid moiety. Moreover, this unique acylation step is required for binding of ghrelin to its receptor (GHSR) and is thought by many to be required for its orexigenic activities (13–15). The vaccines consisted of molecules mimicking the structure of the acylated form of ghrelin and, as intended, led to the production of antibodies that specifically recognized *n*-octanoyl-modified ghrelin. Animals that developed high anti-acylated ghrelin antibody titers had a decreased ratio of brain/plasma total ghrelin levels. Importantly, high anti-acylated ghrelin antibody titers also were associated with decreased body weight gain, decreased adiposity, and decreased feed efficiency (weight gain per kilocalorie of food consumed). In the short observation period of the study, there did not appear to be an effect on reducing food intake.

Ghrelin's Physiologically Relevant Role in Body Weight Control

The study by Zorrilla *et al.* (1) is potentially important for a number of reasons. First, it is supportive of the model predicting a physiologically relevant role for naturally occurring ghrelin in the complex circuitry responsible for coordinated body weight control. Such a notion had been challenged in the first published studies using ghrelin- and GHSR-knockout mice, in which no or only modest differences in body weights were noted between mice lacking ghrelin or the ghrelin receptor and wild-type animals (16–18). However, several recent papers support the idea of a requirement of intact ghrelin signaling for normal body weight homeostasis and the development of diet-induced obesity. For example, Wortley *et al.* (19) demonstrated that mice genetically deficient in ghrelin were leaner than wild-type mice after early exposure to high-fat diet; this was due to an effect on adiposity alone (and not lean mass) and was the result of increased energy expenditure without any changes in food intake. In our own study using GHSR-null mice, we found that ghrelin receptor deficiency was associated with reduced body weight in animals exposed to either high-fat diet or standard

chow; this reduced body weight was due to selective decreases in adiposity and was associated not only with reduced feed efficiency but also with reduced food intake (20). Selective knockdown of GHSR expression in transgenic rats expressing an antisense GHSR transcript also resulted in decreased adiposity and reduced food intake (21). The approach used in the current study may be most similar to the recent study by Shearman *et al.* (22), who used a polyethylene glycol-modified L-RNA oligonucleotide capable of specific high-affinity binding to acylated ghrelin. This compound was infused into animals as a means of reducing the bioavailability of naturally occurring ghrelin and resulted in decreased body weight gain, adiposity, food intake, and feed efficiency. Although these studies used different methods of inactivating normal ghrelin signaling pathways, they all had in common decreased body weight (with a specific effect on fat mass and decrease in lean mass) and increased energy expenditure; the effects on food intake were variable.

The Functional Importance of Ghrelin's Unique Posttranslational Modification

Another key message from the current study by Zorrilla *et al.* (1) is the importance of the acylated-form of ghrelin in ghrelin's actions on body weight homeostasis. Only the two anti-ghrelin vaccines designed to target the *n*-octanoylated form of ghrelin resulted in decreased body weight and decreased feed efficiency; a third vaccine based on the nonacylated, C-terminal portion of ghrelin was ineffective. As mentioned above, acylation has been shown to be required for binding of ghrelin to GHSR (14, 15). However, the necessity of acylation for ghrelin's effects on feeding has been more controversial. For instance, Toshinai *et al.* (23) recently demonstrated that central (but not peripheral) administration of des-acyl ghrelin to ad libitum-fed rats and ad libitum-fed (but not fasted) mice caused increased food intake. Furthermore, i.c.v. des-acyl ghrelin (but not *n*-octanoylated ghrelin) stimulated food intake in GHSR-knockout mice, which suggested the possible existence of another, non-GHSR ghrelin receptor (23). In contrast, Asakawa *et al.* (24) demonstrated that both central and peripheral administration of des-acyl ghrelin to fasted mice inhibited food intake. Similarly, transgenic mice overexpressing des-acyl ghrelin were shown to have both reduced food intake and reduced body weight (24, 25). In yet another example of des-acyl ghrelin's reported effects on food intake, Neary *et al.* (26) demonstrated that i.p. administration of des-acyl ghrelin had neither a stimulatory nor an inhibitory effect on food intake in fasted or fed mice. Although the current study by Zorrilla *et al.* (1) does not fully rectify the discrepancies among the above studies, it does seem to indicate that neutralization of des-acyl ghrelin is not required to obtain the desired decrease in body weight and feed efficiency. Also, it again highlights the functional importance of ghrelin's *n*-octanoyl group and hopefully should prompt more studies to identify the elusive enzyme(s) involved in this unique posttranslational modification.

Inadequacy of Existing Obesity Treatments

The study by Zorrilla *et al.* (1) is also intriguing because of its unique approach to combating obesity. As its increasing prevalence suggests, obesity is quite difficult to prevent, manage, and reverse. Losing weight by dieting often results in rebound weight gain. Notably, such rebound weight gain has been proposed to be due in part to elevated ghrelin levels induced by the initial dieting-associated weight loss (27). Surgery is effective, but is only indicated in individuals with body mass indices ≥40 or ≥35 with comorbid conditions (28, 29). Surgery also comes with significant risk (28). Medications currently approved for obesity are for treatment only, as opposed to prevention, and although they are effective for many people, on average, they do not result in the degree of weight loss ultimately desired. Vaccination as a means of neutralizing or sequestering small,

nonviral, nonbacterial molecules circulating in the bloodstream is a novel approach and is currently being investigated in clinical trials as a treatment for drug addiction.

Who Should Be Vaccinated?

However, despite the data presented by Zorrilla *et al.* (1) supporting the use of methods to neutralize acylated ghrelin by immunopharmacotherapy, many important questions remain. Perhaps the biggest question would be who should be treated. One obvious group of people would be those suffering from Prader–Willi syndrome. These individuals have voracious appetites, hyperphagia, obesity, and sky-high levels of ghrelin (30). Their persistent elevations of ghrelin might warrant a continuous method of inactivating ghrelin, which vaccination theoretically could provide. Perhaps another good candidate group would be individuals with extreme obesity, who are at marked risk for morbidity and mortality but for whom gastric bypass surgery may be too dangerous. For these individuals, the vaccination may partially mimic gastric bypass surgery, which is thought to involve not only restrictive and malabsorptive mechanisms of inducing weight loss but also hormonal changes that influence body weight, including marked reductions in circulating ghrelin levels (27).

Another question is how long the immunoneutralization would be efficacious. For example, it is conceivable that antibody titers could wane over time, thereby resulting in less inhibition of ghrelin action. On the other end of the spectrum, the vaccination's efficacy might be long-lasting, which could be problematic if its effects were irreversible. For example, might vaccination work so well as to result in cachexia? Considerations regarding the long-term effects of prolonged and presumably irreversible ghrelin neutralization also would need to be made before vaccinating individuals wanting to prevent the development of obesity. Nonetheless, if vaccination against acylated ghrelin had a similar effect in obese humans as it did in nonobese mice in terms of decreasing body weight and feed efficiency, it might prove to be a welcome new agent in the physician's tool box to combat obesity and related comorbidities.

Footnotes

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